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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/047,652	03/25/98	PAPADOPOULOS V	009/064/SAP

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EXAMINER	
DAVIS, M	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 04/12/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12-11-99.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 48-52 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 48-52 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 1-47, and adds new claims 48-52, which are related to claims 1-47, and are not new matters,

Accordingly, claims 48-52 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 48-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 48-52 are drawn to an antisense oligonucleotide complementary to a PBR DNA or RNA, wherein said antisense oligonucleotide inhibits or reduces the expression of PBR, and is capable of homologously recombining with PBR DNA.

1) It is unpredictable whether an antisense oligonucleotide complementary to a PBR DNA or RNA is capable of homologous recombination with PBR DNA in cells. Papadopoulous et al, of record, (see Office Action paper No:8), teach that to contruct the vector for testing homologous recombination, the 1.15 kb *neo* gene is positioned in between the two large PBR genomic DNA fragments, wherein the first fragment spans the exon 2, intron 2, and the first 42 bp of exon 3, and the second fragments spans 117 bp of exon 3, intron 3, and the first 270 bp of exon 4 (p.32130). In other words, two very large fragments of PBR DNA are flanking the 1.15 kb *neo* gene. Weiss, PN= 5,840,708 teach that the preferred length of an antisense oligonucleotide is 20 nucleotides (column 10). Presumably, the claimed vector for testing homologous recombination in cells comprises two PBR antisense oligonucleotides, each having about 20 nucleotides, and flanking the 1.15 kb *neo* gene. The DNA fragment comprising two PBR antisense oligonucleotides, each having about 20 nucleotides, and flanking the 1.15 kb *neo* gene, would have very little similarity with the PBR gene, due to the presence of the 1.15 kb *neo* gene. It is unpredictable whether said DNA fragment could have stable hybridization with PBR genomic DNA or mRNA, due to its low similarity with the PBR gene, and possible hindrance by the overwhelmingly large 1.15 kb *neo* gene relative to the total of 40 nucleotides of the antisense oligonucleotides. Without stable hybridization, it is questionable whether homologous recombination could occur. Yet the specification does not discloses how to test for the homologous recombination of the claimed antisense oligonucleotide. The specification fails to provide an enabling disclosure for an antisense oligonucleotide complementary to a PBR DNA or RNA, which is capable of

homologous recombination with PBR DNA in cells. The specification provides insufficient guidance with regards to these issues, and provides no working examples of an antisense oligonucleotide complementary to a PBR DNA or RNA, which is capable of homologous recombination with PBR DNA in cells. Although working examples are usually not required, but in the presence of the above unpredictability, in view of the fact that one of skill in the art does not have knowledge of an antisense oligonucleotide complementary to a PBR DNA or RNA, which is capable of homologous recombination with PBR DNA in cells, undue experimentation would be required to practice the claimed invention.

2) Claims 48-52 read on an antisense oligonucleotide complementary to a PBR DNA or RNA, wherein said antisense oligonucleotide inhibits or reduces the expression of PBR *in vivo*.

It is unpredictable that an antisense oligonucleotide complementary to a PBR DNA or RNA could inhibit or reduce the expression of PBR *in vivo*. Branch A.D., 1998, TIBS 23: 45-50 teaches that the ability of an antisense oligonucleotide to eliminate the function of a single gene has never been tested. Weiss, 1998, PN=5,840,708 teaches that although the use of antisense oligonucleotides for therapeutic purposes has been successfully accomplished *in vitro*, successful application of antisense therapy *in vivo* has been extremely limited, and that there are only a few reports of modulation of various pathological conditions by antisense therapy in rodents. Weiss teaches that even if biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed (columns 2-3). Thus, given the unpredictability of the behavior and effects of antisense

oligonucleotide *in vivo*, it is unpredictable whether the claimed antisense oligonucleotide would inhibit or reduce the expression of PBR *in vivo*. The specification fails to teach the sites within the mRNA encoding region of all of the antisense oligonucleotides encompassed within the claims which would be expected to function as an effective antisense binding site. It was well known in the art at the time the invention was made that identification of such binding sites in a given mRNA species resulting in inhibition of gene expression is an unpredictable art. For instance, US Patent No. 5,585,479 discloses an effective oligonucleotide and show that moving the target just one or two bases, can greatly reduce of even eliminate, antisense activity (data disclosed in columns 15-17). US Patent No. 5,585,479 states that "there are no rational explanations or rules that would predict active sequences". Thus, in view of the unpredictability of whether all antisense molecules would function effectively to inhibit gene expression of the target PBR, and in the absence of evidence to the contrary, a skilled artisan would be unable to practice the claimed invention, using antisense sequences without undue experimentation and with a reasonable expectation of success.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

If applicant were able to overcome the above rejection under 35 USC 12, first paragraph, enablement, as applied to claims 48-52, claim 48 would still be rejected under 35 USC 112, first paragraph, scope.

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an inhibitor of the expression of PBR by homologous recombination, does not reasonably provide enablement for a non-naturally occuring compound which inhibits or reduces the expression of PBR. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 48 is drawn to a non-naturally occuring compound which inhibits or reduces the expression of PBR.

For the interest of examination purposes, it is assumed that a non-naturally occuring compound is any compound that could be synthesized. In addtion, claim 48 reads on a non-naturally occuring compound which inhibits or reduces the expression of PBR both *in vitro* and *in vivo.*

The specification discloses that agents that inhibit PBR expression include, but are not limited to, antisense oligonucleotides, antibodies, or lipids (p.26-27). Given the broadest interpretation of the language "not limited to", the claim 48 reads on any synthetic compounds that inhibit the expression of PBR. The specification however does not disclose the structure or sequences of antisense oligonucleotides. The specification fails to teach the sites within the mRNA encoding region of all of the antisense oligonucleotides encompassed within the claims which would be expected to function as an effective antisense binding site. It was well known in the art at the time the invention was made that identification of such binding sites in a given

mRNA species resulting in inhibition of gene expression is an unpredictable art, *supra*. In addition, the specification does not disclose whether lipids could actually inhibit the expression of PBR *in vivo*. The specification does not disclose the concentration of lipids necessary for *in vivo* inhibition of PBR expression, nor how the administered lipids could reach the target cells *in vivo* for inhibition of the expression of PBR. Without sufficient guidance, one of skill in the art would not know how to use lipids for inhibiting the expression of PBR *in vivo*. In view of the above unpredictability, and insufficient guidance, undue experimentation would be required to make and use the claimed composition as broadly as claimed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, NEW REJECTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 48-52 are drawn to a non-naturally occurring compound, which inhibits or reduces the expression of PBR. Said compound could be an antisense oligonucleotide, which is capable of homologously recombining with a PBR DNA.

1. The specification describes that the PBR sequences for human, mouse and bovine are known, and that antisense oligonucleotide complementary to PBR DNA or RNA sequences could be administered to inhibit or reduced the translation of PBR (p.26). The specification however does not disclose the structure or the sequence of the antisense oligonucleotides, which inhibit or reduce the expression of PBR *in vivo*, and are capable of homologous recombination with a PBR DNA. Although antisense oligonucleotide sequences complementary to any gene could be routinely synthetized based on the known structure of the gene, and could be successfully used for

inhibiting the expression of said gene *in vitro*, as taught by Weiss, *supra*, it is unpredictable that an antisense oligonucleotide complementary to a PBR DNA is capable of homologous recombination with PBR DNA in a cell, *supra*. Further, as taught by US Patent No: 5, 585, 479, there are no rational explanations or rules that would predict active antisense sequences, *supra*. Since the specification fails to describe the structure of the claimed antisense oligonucleotides, that could inhibits or reduce the expression of PBR *in vivo* and are capable of homologous recombination, it is clear that the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Thus, there is insufficient support of claims 48-52 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

REJECTION UNDER 35 USC 102

1. Claims 48, 49, 51, and 52 are rejected under 35 USC 102(a), as being anticipated by Papadopoulous et al, *supra*, for the same reasons set forth in the rejection of claims 1, 4, 20, 37, 39, and 43 over this reference in the Office action paper No: 8.

Applicant adds new claims 48, 49, 51, and 52, which are drawn to a non-naturally occuring compound which inhibits or reduces the expression of peripheral-type benzodiazepine receptor (PBR). Said compound is a nucleic acid sequence, contained in a vector, and is capable of homologously recombining with a PBR DNA.

For the interest of examination purposes, it is assumed that a non-naturally occuring compound is any compound that could be synthesized.

Applicant further discloses that a Katz declaration by applicant will be submitted to obviate this rejection.

Rejection remains, because the Office has not received the declaration by applicant. The replacement vector taught by Papadopoulous et al is a non-naturally occurred nucleic acid sequence, which disrupts the expression of PBR by a homologuous recombination process. In other words, the replacement vector taught by Papadopoulous et al is the same as the claimed invention.

2. Claim 48 is rejected under 35 USC 102(a), as being anticipated by Moser et al, or Garnier et al, of record in paper No:8, for the same reasons set forth in the rejection of claims 1, 4, 20, 37, 39, and 43 over this reference in the Office action paper No: 8.

For the interest of examination purposes, it is assumed that a non-naturally occuring compound is any compound that could be synthesized.

Applicant adds new claim 48, which is drawn to a non-naturally occuring compound which inhibits or reduces the expression of peripheral-type benzodiazepine receptor (PBR).

Rejection remains because the compound Ro5-4864 taught by Moser et al, or Garnier et al is a non-naturally occured compound which inhibits the expression of PBR.

REJECTION UNDER 35 USC 103, NEW REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casalotti, SO, 1992, Gene, 121(2): 377-382, in view of Weiss, US PN= 5,840,708, and Lu C et al, 1996, Clin Cancer Res, 2(8): 1417-25.

For the interest of examination purposes, it is assumed that a non-naturally occuring compound is any compound that could be synthesized.

Claims 48-51 are drawn to a non-naturally occuring compound which inhibits or reduces the expression of peripheral-type benzodiazepine receptor (PBR). Said compound coud be an antisense oligonucleotide complementary to a PBR DNA or RNA, wherein said antisense oligonucleotide inhibits or reduces the expression of PBR. Said antisense oligonucleotide is

contained in a vector. Claims 48-51 read on an antisense oligonucleotide complementary to a PBR DNA or RNA, wherein said antisense oligonucleotide inhibits or reduces the expression of PBR *in vitro*. In addition the specification discloses that compounds that inhibit PBR expression include antibodies.

Casalotti et al teach structure of rat PBR gene.

Weiss teaches how to make antisense oligonucleotides (columns 9-12). Weis teaches that antisense oligonucleotides targeted to any known nucleic acid sequence can be prepared by oligonucleotide synthesis (column 9). Weiss further teaches that synthetic antisense oligonucleotides for therapeutic purposes has been successfully accomplished *in vitro*, and within cultured cells (column 2).

Lu et al teach that clones transfected with antisense IL-6 expression vector manifest a decrease in IL-6 gene expression.

The art establishes that it was possible at the time the invention was made to make antisense oligonucleotides targeted to any known nucleic acid sequence. The art further teaches rat PBR gene structure. The art also teaches that the use of antisense oligonucleotides have been successfully accomplished *in vitro* against target genes, wherein the antisense oligonucleotide could be expressed in an expression vector. In addition, it is well known in the art that antagonist antibodies against a protein could be routinely made.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to synthesize an antisense oligonucleotide complementary to a

PBR DNA or RNA, because the structure of rat PBR gene is known, as taught by Casalotti et al, and because antisense oligonucleotides targeted to any known nucleic acid sequence can be prepared by oligonucleotide synthesis, as taught by Weiss. One of ordinary skill in the art would have expected that the synthesized antisense olignucleotide complementary to PBR DNA or RNA would inhibit expression of PBR *in vitro*, because the use of antisense oligonucleotides have be successfully used *in vitro* against target genes, as taught by Weiss. It would have been obvious to express the antisense oligonucleotide in a vector to inhibit PBR gene expression *in vitro*, because such method is routine in the art, as taught by Lu et al. One of ordinary skill in the art would have been motivated to make an antisense oligonucleotide complementary to a PBR DNA or RNA, with a reasonable expectation of success.

All other rejections in the Office action of paper No:8 are withdrawn. NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 10:00 am to 2:00 pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Toni Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

March 8, 2000

SUSAN UNGAR
PATENT EXAMINER